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In silico assessment of the inhibitory effect of four flavonoids (chrysin, naringin, quercetin, kaempferol) on tyrosinase activity using the MD simulation approach

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Abstract

Tyrosinase is a tetrameric enzyme that plays an important role in pigment production. Overproduction of melanin, which may lead to several skin disorders, is a result of tyrosinase activity. Hence, tyrosinase inhibitors are of key importance in the treatment of these disorders. In the present study, four flavonoid inhibitors, namely chrysin, naringin, quercetin, and kaempferol, were evaluated physiochemically, and the inhibitory effects of these compounds on tyrosinase activity were evaluated using the molecular dynamics (MD) simulation method. To create the best conformation of the enzyme-substrate/inhibitor, the docking process for enzyme-substrate, i.e., enzyme-chrysin, enzyme-quercetin, enzyme-naringin, and enzyme-kaempferol, was performed. The complexes with the best binding energies were selected as the models for the MD simulation process. Furthermore, the structural (RMSD, Rg, RMSF, and Distance) and the thermodynamics properties of the complexes were evaluated. Additionally, the PMF was conducted to calculate the binding free energies. The results showed that chrysin, quercetin and the substrate were at similar distances to the amino acids of the active site, but naringin and kaempferol were closer to the active site of the enzyme than the substrate. Moreover, the analysis of the binding energy revealed that the substrates, chrysin, kaempferol, quercetin, and naringin bound to the enzyme with binding energies of −7.8, −3.1, −7.1, −3.9, and −8.4 kcal/mol, respectively, which confirms that naringin has the highest inhibitory effect on tyrosinase among other inhibitors, which makes it an appropriate candidate as a whitening agent in skin disorders.

Key words: tyrosinase, chrysin, quercetin, kaempferol, naringin, MD simulation

Abbreviations

COM	– center of mass	RMSF	– root mean square fluctuation
L-DOPA	– L-3,4-dihydroxyphenylalanine	RMSD	– root mean square deviation
MD	– molecular dynamics	Rg	– radius of gyration
PDB	– protein data bank	TIP3P	– transferable intermolecular potential with 3 points
PMF	– potential of mean force	WHAM	– weighted histogram analysis method

Introduction

Tyrosinase is a tetrameric (H_2L_2) copper-containing enzyme with significant catalytic functions in pigment production. The enzyme has molecular weight of 120 kDa with two heavy (H) and two light (L) subunits of 43 and 14 kDa, respectively. Subunit H, contrary to subunit L, consists of an active site for copper ions (Hassani et al., 2018; Taherkhani and Gheibi, 2014). The enzyme has multiple catalytic functions, including mono-oxygenase (cresolase) activity (hydroxylation of monophenols to *o*-diphenols) and catechol oxidase activity (oxidation of *o*-diphenols to *o*-quinone) (Yin et al., 2011). Three con-

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